Mini-Sentinel Methods: Accomplishments and lessons learned
(with comments about the Vaccine Safety Datalink)

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June 3, 2011
Agenda

• Framework for post-marketing surveillance
• Vaccine Safety Datalink (VSD)
• Mini-Sentinel methods development to date
  – Data capacity
  – Distributed methods
  – Signal alerting strategies
• Needs and recommendations
### Stages of post-marketing surveillance

#### Aim:
- **Identify excess risk**
  - Aim = Identify excess risk
  - Approach = Consider many AEs or AE:product pairs (100’s, 1000’s)

#### Method:
- **Signal Generation**
  - Specific AE:product pairs of prior concern
  - Approach = Repeated monitoring or one-time expedited analysis of AE:product pairs (typically 5-10)
  - Example = Data mining of spontaneous reports

- **Signal Refinement**
  - Specific AE:product pairs of prior concern
  - Approach = Repeated monitoring or one-time expedited analysis of AE:product pairs (typically 5-10)
  - Example = Active surveillance in Mini-Sentinel and VSD using coded electronic health information

- **Signal Evaluation**
  - A highly suspected AE:product pair
  - Approach = One-time, in-depth and rigorous investigation of a single pair
  - Example = Retrospective, formal epidemiological study using individual-level data, validated AEs, richer confounders
Sentinel Initiative Vision*

- System will be able to refine safety signals in near real-time. This will require the following capabilities:
  - rapidly defining exposed cohorts;
  - establishing algorithms to capture health outcomes of interest;
  - using sophisticated modular programs capable of running evaluations with minimal input from epidemiologists and clinicians and limited or no ad hoc programming; and
  - developing a framework to guide methodological approaches for safety surveillance evaluations that include confounding adjustment.

- Approaches for signal generation will be under development.

* Within the next 3 years
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### Applications

- Oral antidiabetic agents and MI, rotavirus vaccine and intussusception, etc.
VSD: Data capacity

- **Integrity**
  - Quality of HMO vaccine database (Mullooly et al., AJE 1999)
  - Predictive value of seizure ICD-9 code (Shui et al., Vaccine 2009)
  - Accuracy of flu vaccine data in MCOs (Sy et al., Vaccine 2010)

- **Accessibility**
  - Rapid assessment of flu vaccine coverage (Lewis et al., MMWR 2005)
  - Active surveillance pilot to detect early signals (Davis et al., Epidemiol 2005)
  - VSD near real-time model & infrastructure (Baggs et al, Pediatrics 2011)

- **Diversification**
  - Enhancing detection w/EMRs (Hinrichsen et al., J Am Med Inform Assoc 2007)
  - Detecting vaccine AEs in clinical notes (Hazelhurst et. al. Vaccine 2009)
VSD: Distributed analysis methods & applications

- Developed a **prospective safety monitoring** framework
  - Real-time vaccine safety surveillance (Lieu et al., Med Care 2007)
  - Near real-time flu vaccine safety surveillance (Greene et al., AJE 2010)

- A system is emerging for **rapid signal evaluation**
  - Lessons learned to reduce false positives (Yih et al., Pediatrics 2011)

- Have evaluated these systems via **applications in practice**
  - MMRV and febrile seizures (Klein et al., Pediatrics 2010)
  - Rotavirus vaccine & intussusception (Belongia et al., Ped Inf Dis 2010)
  - Tdap safety in adolescents and adults (Yih et al, Vaccine 2009)
  - Ongoing: HPV, Pentacel, Kinrix, PCV13, others...
VSD: Alerting strategies

- **Study design**
  - Comparing designs for active surveillance (McClure et al., Vaccine 2008)
  - Self-controlled case series risk windows (Xu et al., Stat in Med 2010)

- Extending **sequential methods** to observational safety setting
  - Continuous monitoring with maxSPRT (Kulldorff et al., Seq Anal 2011)
  - Accounting for uncertainty in hx controls (Li et al., Stat in Med 2010)
  - Sequential design/analysis challenges (Nelson et al., submitted)
  - Group sequential designs simulation evaluation (Zhao et al., submitted)

- Improving methods for **confounder adjustment**
  - Propensity score stratification (Li et al., accepted at Stat in Biosciences)
  - Regression, generalized estimating equations (Cook et al., submitted)

- Improving method to handle **data complexities**
  - Partially-accrued and missing data (Greene et al., in press at PDS)
VSD: Methods challenges and priorities

- **Challenges**
  - Optimizing methods given rare AEs, variable uptake, site heterogeneity
  - False positive/negative signals due to misclassification & confounding
  - Best practices for rapid signal evaluation and follow-up
  - Detecting unanticipated AEs

- **Priorities**
  - Enhance, customize and evaluate more sequential approaches
    - exact tests, delayed starts, risk differences, longer-term outcomes
  - Develop methods to better account for misclassification & confounding
    - sequential 2-phase sampling (to get better AE, confounder data)
    - analysis (vs. design) based confounding adjustment, use of propensity scores
  - Solidify system for rapid signal evaluation
  - Evaluate and implement data mining approaches for signal generation
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### Current DPs
- Aetna
- HealthCore
- HMORN
- Humana
- KP
- Vanderbilt

### New DPs
Data Capacity

- **Data validation and adjudication**
  - Validation of selected health outcomes of interest (HOI):
    - Myocardial infarction
    - Severe liver injury
    - Anaphylaxis
    - Venous thromboembolism
    - Intussusception

- **Literature reviews on the validity of HOI identification**
  - Review of 20 HOIs completed (accepted at PDS 2011)
  - Review of 20 additional HOI in progress
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**Applications**

• Oral antidiabetic agents and MI, rotavirus vaccine and intussusception, etc.
Distributed methods

- Distribution and retrieval
  - Developed increasingly complex query modules
  - Fast turn-around

- Anonymous linkage across sources
  - Of great importance when adding clinically rich data sources to the longitudinal claims data backbone
  - Have identified a candidate method
  - Working group to evaluate such method (starts in June)
Distributed methods

- Evaluating strategies for accessing distributed data (RFTO) (Rassen et al PDS 2010, Med Care 2010, ISPE workshop etc)
  - That allow multivariable confounder balancing
  - That use varying information content to a maximum
  - That allow flexible subgroup analyses
  - Preserve patient privacy
  - Respects plan confidentiality
  - (Velentgas et al. PDS 2008, Rassen et al PDS 2010, Med Care 2010, ISPE workshop etc)

- Provide guidance for MS on valid and practical strategies
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Design and validity

- Taxonomy project:
  - Expedited choice of design and analytic monitoring approach
  - Identified generic attributes of exposure, outcomes, and relationships
  - Have developed a decision table for fundamental design choice and Year 2 Taxonomy is working on analytic choices

- Self-controlled designs:
  - Came up with clear guidance on (Maclure et al, submitted)
    - Strength/limitations, practicability in a monitoring setting
  - Tested a multivariate SCCS approach (Madigan et al, submitted)
Design and Validity

- Automated covariate adjustment
  - Empirical covariate identification in claims data is essential
    - for improved confounding adjustment
    - for rapid turn-around
  - Empirical approaches have been shown to be superior to investigator identified adjustment in claims
  - Simulation studies have shown that theoretical biases (M-Bias and z-Bias) are not relevant (Myers et al. AJE 2011 in press)
  - A comprehensive approach to automated covariate adjustment is developing for PS and DRS methods (Rassen&Schneeweiss, submitted)
Performance of signal alerting algorithms

- Sequential testing
  - Developed guidance on sequential designs customized for observational safety settings (Nelson et al, submitted)
  - Reviewed methods ‘state-of-the-art’
    - Group sequential LRT (inc. maxSPRT, Kulldorff et. al Seq Anal 2011)
    - Conditional sequential sampling procedure (Li et. al Stat Med 2009)
    - Clinical trial group sequential methods (Lan&Demets Stat Med 1994)
    - Estimating equations approach (Cook et al, submitted)
  - Simulation to compare performance (Cook et al, submitted)
    - Type 1 error rate, power, time-to-signal detection
    - Varying outcome prevalence, exposure & confounder complexity
  - Using inverse probability weighting (ongoing Y2 activity)
Performance of signal alerting algorithms

- Non test-based approaches (Pilot)
  - Are available but fair comparisons in a monitoring setting are lacking
  - Pilot work has set up a simulation framework and evaluation statistic (Gagne et al.)

- Safety monitoring and decision science (Pilot)
  - MS recognizes the value of decision analytic approaches in an active surveillance system
  - Pilot work on alerting based on the future value of continued monitoring (Patrick et al.)
Performance of signal alerting algorithms

- Rapid signal validation techniques (WG starting)
  - Develop a framework for follow-up to alerts resulting from signal refinement
    - Data checks
    - Program checks
    - Sensitivity analyses
    - Additional confounding control
    - Endpoint adjudication etc.
Special Aspects

- Vaccines (see VSD)

- Devices
  - Data issues
  - Rapidly changing technologies
  - Exposure-risk window (implantation vs. device itself)

- In-hospital products
  - Data issues
  - Temporality issues
  - Exposure-risk window (end at discharge or later)